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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 0 3 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Review of a Two-Generation Reproduction Study in Rats Fed with Diuron (Guideline 83-4)

TO: Carol Peterson/Walter Waldrop PM-71
RD (H-7508W)

FROM: David S. Liem, Ph.D. David Shiem 10/1/92
Section II, Toxicology Branch II/HED (H7509C)

THROUGH: K. Clark Swentzel, Section Head K. Clark Swentzel 10/2/92
Section II, Toxicology Branch II/HED (7509C)
and
Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 10/5/
Toxicology Branch II/HED (H7509C)

MRID#: 419573-01 DP BARCODE#: D167256 PC#: 035505

SUBMISSION#: S400511 CASWELL NO.: 410 HED Project#: 1-1984

ACTION REQUESTED : To review a study entitled "Reproductive and Fertility Effects with Diuron (IN 14740), Multigeneration Reproduction Study in Rats" submitted by E.I. Dupont de Nemours.

CONCLUSIONS: In a two-generation reproduction study, Crl:CDBR rats were fed diuron in the diet at dosage levels of 0, 10, 250, or 1750 ppm (during premating, for males an average of 0.68, 16.9, and 120 mg/kg/day and for females an average of 0.80, 20.3, and 144 mg/kg/day, respectively for both generations).

Compound-related parental toxicity was observed at 1750 ppm as evidenced by decreased body weight, body weight gain, and food consumption in both sexes and generations. The parental toxicity NOEL and LOEL were 250 and 1750 ppm, respectively.

Compound-related reproductive toxicity was observed at 1750 ppm as evidenced by decreased pup body weight during the lactation period for both sexes and generations. The reproductive toxicity NOEL and LOEL were 250 and 1750 ppm, respectively.

CLASSIFICATION: Core-minimum. This study satisfies the requirements of Subdivision F Guideline 83-4 for a two-generation reproduction study in rats.

DOC930182
FINAL

DATA EVALUATION REPORT

DIURON

Study Type: Reproductive Toxicity

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer	Pia Lindström, DPH	Date	9/30/92
Independent Reviewer	Sanju Diwan, Ph.D.	Date	9/30/92
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Contract Number: 68D10075
Work Assignment Number: 1-121
Clement Number: 93-102
Project Officer: James Scott

.EPA Reviewer

Approved by: David Liem, Ph.D. Signature: David Liem
Review Section II, Toxicology Branch II/HED Date: 10/1/92

EPA Section Head: Clark Swentzel Signature: K. Clark Swentzel
Review Section II, Toxicology Branch II/HED Date: 10/2/92

DATA EVALUATION REPORT 009786

STUDY TYPE: Two-Generation Reproductive Toxicity Study; Guideline 83-4

EPA IDENTIFICATION NUMBERS

TOX CHEM. NUMBER.: 410

MRID NUMBER.: 419573-01

TEST MATERIAL: Urea, N'-(3,4-dichlorophenyl)-N,N-dimethyl-

SYNONYMS: IN 14740-155; Diuron; Chlorfenidim; Cekiuron; Crisuron; Dailon; Diater; Drexel Diuron 4L; Farmco Diuron; Herbixol; Tigrex; Unidron; Vonduron

SPONSOR: Du Pont Agricultural Products, E. I. du Pont de Nemours and Company, Wilmington, DE

STUDY NUMBER: HLR 560-90

TESTING FACILITY: E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE

TITLE OF REPORT: Reproductive and Fertility Effects with Diuron (IN 14740), Multigeneration Reproduction Study in Rats

AUTHOR: J.C. Cook

REPORT ISSUED: December 14, 1990

CONCLUSIONS: In a two-generation reproduction study, Crl:CD®BR rats were fed diuron in the diet at dosage levels of 0, 10, 250, or 1,750 ppm (during premating, for males an average of 0.68, 16.9, and 120 mg/kg/day and for females an average of 0.80, 20.3, and 144 mg/kg/day, respectively for both generations). Compound-related parental toxicity was observed at 1,750 ppm as evidenced by decreased body weight, body weight gain, and food consumption in both sexes and generations. The NOEL and LOEL for parental toxicity were 250 and 1,750 ppm, respectively.

Compound-related reproductive toxicity was observed at 1,750 ppm as evidenced by decreased pup body weight during the lactation period for both sexes and generations. The NOEL and LOEL for reproductive toxicity were 250 and 1,750 ppm, respectively.

CLASSIFICATION: CORE Guideline Data. This study meets the requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats.

A. MATERIALS

Test Compound

Purity:	97.1%
Description:	White crystals
Lot number:	8805540
Date Received:	Not reported
Contaminants:	Not reported

Vehicle: None used; the test material was administered in the diet.

Test Animals

Species:	Rat
Strain:	Crl:CD®BR
Source:	Charles River Laboratories, Raleigh, NC
Age:	F_0 males--approximately 60 days at start of study
	F_0 females--approximately 57 days at start of study
Weight:	F_0 males--311.0-394.5 g at start of study
	F_0 females--189.3-252.7 g at start of study

B. STUDY DESIGN

This study was designed to assess the potential of diuron to cause reproductive toxicity when administered continuously in the diet for two successive generations.

Mating: After 23 days of acclimatization followed by 73 days of dietary treatment, the F_0 females were mated with males from the same group in a ratio of 1:1 until evidence of mating (vaginal plug or presence of sperm in a vaginal smear) was obtained or for a maximum of 21 days. The day on which mating was confirmed was designated day 0 of gestation. The F_1 animals were mated in a similar fashion following 105 days on the test diet. Sibling matings were avoided.

Environmental conditions: A 12/12 hour light/dark cycle was maintained. The temperature was 21-25°C; the humidity was 40-60%.

Group arrangement: Parental animals were distributed amongst four groups using a computer-generated randomization based on body weight as follows:

Test Group	Dietary Level (ppm)	Number Assigned per Group F_0		F_1	
		Males	Females	Males	Females
Control	0	30	30	30	30
Low dose	10	30	30	30	30
Mid dose	250	30	30	30	30
High dose	1,750	30	30	30	30

Dosage administered: The test material was administered continuously in the diet (Purina® Certified Rodent Chow #5002) for two consecutive generations. The test diets were adjusted for purity. Diets were prepared weekly and stored in a refrigerator until used. The test material was mixed with irradiated rodent chow for three minutes in a high-speed mixer. The purity of the test material was confirmed three times during the study. Stability, concentration, and homogeneity of the test material in the diet were analyzed prior to start of the study. Stability was analyzed after storage in a refrigerator for 14 days or at room temperature for 7 and 14 days. In addition, concentration analyses of the test material in the diet at all dosage levels were conducted three times during the study.

Dosage rationale: Dosages were selected based upon several previous studies with diuron. Sprague-Dawley rats fed diuron for two years exhibited body weight and hemoglobin decreases at 250 ppm and bladder hyperplasia at 2,500 ppm (1963); Sprague-Dawley rats fed diuron for only 90 days exhibited a body weight decrease at 2,500 ppm, while decreased red blood cell count and increased bone marrow hyperplasia were evident at 250 and 2,500 ppm (1963). A two-year feeding study in Wistar rats showed a decrease in body weight and an increase in bladder neoplasia at 250 ppm and an increase in anemia at 25 ppm (1985). A one-month pilot feeding study, conducted prior to the present study, showed decreases in body weight and weight gain at 2,500 ppm.

Observations: Observations for mortality, moribundity, and overt signs of toxicity were conducted at least once a day. A more detailed clinical examination was performed weekly. Food consumption was measured weekly; for females during gestation, it was determined on days 0, 7, and 14 (it was not determined during lactation). Body weight data were recorded weekly; for females during gestation and lactation, data were recorded on days 0, 7, 14, and 21. Terminal body weight data were recorded for all animals.

The following data were recorded for each litter:

- Number of live and dead pups, pup weight (collectively by sex), sex, and external abnormalities at birth and on lactation days 4, 7, and 14

- Number of live and dead pups, individual pup weight, external abnormalities, and sex at weaning on lactation day 21

- Daily clinical signs

On lactational day 4, pups were randomly culled to 4/sex/litter whenever possible; culled pups were sacrificed and discarded. Pups found dead were necropsied. Thirty male and thirty female F_1 pups were randomly selected as F_1 parental animals. Twenty pups per sex, group, and generation were randomly selected for a complete necropsy. The remaining pups were sacrificed and discarded.

Parental animals found dead or sacrificed moribund and females that did not deliver were necropsied. Parental F_0 and F_1 animals were sacrificed and subjected to a gross pathological examination (F_0 males and females after 119-120 and 117-132 days of feeding, respectively; F_1 males and females after 158-167 and 151-177 days of feeding, respectively). The following tissues were collected and examined histologically at the control and high-dosage levels (gross lesions from all dosage levels were examined):

- Coagulating gland
- Seminal vesicles
- Prostate
- Uterus
- Ovaries
- Gross lesions
- Testes
- Epididymides
- Vagina
- Pituitary

Testis weight data were also recorded.

Statistical analysis: The following analyses were conducted.

- Body weight, body weight gain, food consumption, organ weights and length of gestation--Bartlett''s test for homogeneity of variances, ANOVA, and Dunnett's test for pairwise comparisons between groups

- Incidences of clinical, gross and microscopic observations--Fisher's Exact test with/without Cochran Armitage trend test

- Mating, fertility, and gestation indices and litter survival--Fisher's Exact test

- Pup numbers, survival, and weights and viability and lactation indices--Mann-Whitney U test

- Significance was judged at alpha = 0.05.

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated December 20, 1990, was provided.

- A signed Statement of Compliance with EPA GLPs, dated December 13 and 20, 1990, was provided.

- A signed Quality Assurance Statement, dated December 12, 1990, was provided.

C. RESULTS

Test Material Analysis: The purity of the compound was 95%-100% of target. Concentrations of the test material in the diets were 91%-115% of nominal values. Homogeneity analyses revealed concentrations of 95%-105% of nominal values; stability analyses were 85%-103% (after 14 days at room temperature) of nominal values.

Parental Toxicity

Mortality: No compound-related mortalities were observed. Incidental deaths/moribund sacrifices are described below.

In the F_0 generation, one female from the control group was sacrificed _in extremis_ due to difficulties at the time of delivery. One female from the 10-ppm group was found dead; necropsy did not reveal cause of death.

In the F_1 generation, three males, one each from the control group, 250-ppm group, and 1,750-ppm group were found dead. The control animal had kidney cysts; necropsies of the other two males did not reveal cause of death.

Clinical observations: No compound-related clinical signs were observed in any sex and generation.

Body weight: Compound-related effects in body weight and body weight gain were observed at 1,750 ppm in both sexes and generations. Significant differences from controls observed at 10 and 250 ppm were considered to be incidental. Summaries of body weight gain from selected time intervals are presented in Tables 1, 2, and 3. Detailed results are presented in the text.

In the F_0 generation among males at 1,750 ppm body weight (data not shown) decreased significantly by an average of 7% starting on day 7. Body weight gain (Table 1) among males decreased significantly at 250 ppm on days 91-98 (18%) and at 1,750 ppm on days 0-14 (21%), 21-28 (15%), 42-49 (28%), 77-84 (53%), 91-98 (90), 0-70 (premating; 16%), 70-112 (mating and postmating; 28%), and 0-112 (entire feeding period; 18%). Incidental, but significant, increases were noted at 10 ppm on days 14-21, 35-42, and 63-70 and at 250 ppm on days 35-42, 63-70, and 91-98.

Among F_0 females at 1,750 ppm, body weight (data not shown) decreased significantly by an average of 7% starting on day 7 during premating and by 9% during the gestation and lactation periods. Body weight gain (Table 1) among females decreased significantly at 1,750 ppm on days 0-7 (48%), 21-28 (69%), and 0-70 (premating; 28%). No body weight gain differences were noted between groups during the gestation period (Table 2). Significant increases in body weight gain were observed at 1,750 ppm during the lactation period on days 0-7 and 0-21 (Table 3).

In the F_1 generation among males at 1,750 ppm body weight (data not shown) decreased significantly by an average of 16% starting on day 0. Body weight gain (Table 1) among males decreased significantly at 250 ppm on days 63-70 (33%) and 147-154 (52%) and at 1,750 ppm on days 0-28 (16%), 42-49 (20%), 63-70 (26%), 91-98 (46%), 147-154 (72%), 0-105 (premating; 15%), 105-161 (mating and postmating; 41%), and 0-161 (entire feeding period; 17%).

Among F_1 females at 1,750 ppm body weight (data not shown) decreased significantly by an average of 16% starting on day 0 during premating; by 14% during the gestation period; and by 19% during the lactation periods. Body weight gain (Table 1) among females decreased significantly at 250 ppm on days 0-7 (11%) and 14-21 (12%) and at 1,750 ppm on days 0-14 (17%) and 0-105 (premating; 14%); it increased significantly at 10 ppm on days 70-77. During gestation, body weight gain decreased significantly on days 14-21 (21%) and 0-21 (19%) (Table 2). During the lactation period, significant increases in body weight gain were observed at 1,750 ppm on days 0-7, 14-21, and 0-21 (Table 3).

Food consumption: Compound-related effects on food efficiency were observed at 1,750 ppm in F_0 males and females and in F_1 females. Significant differences from controls observed at 10 and 250 ppm were considered to be incidental. Summaries of food efficiency (g weight gain/g food consumed) from selected time intervals are presented in Tables 4 and 5. Detailed results are presented in the text.

In the F_0 generation among males at 1,750 ppm food consumption (g/animal/day; data not shown) decreased significantly on days 0-14, 21-28, 42-56, and 0-70. Food efficiency (Table 4) decreased significantly at 10 ppm on days 42-49 and at 1,750 ppm on days 0-14, 42-49, and 0-70. It increased significantly at 10 ppm on days 63-70; at 250 ppm on days 35-42 and 63-70; and at 1,750 ppm on days 63-70.

Among F_0 females at 1,750 ppm food consumption (data not shown) decreased significantly on days 0-7, 21-28, 35-49, and 0-70. During gestation food consumption decreased consistently at 1,750 ppm. Food efficiency among females (Table 4) decreased significantly at 1,750 ppm on days 0-7, 21-28, and 0-70. It increased significantly at 10 ppm on days 0-7. During gestation no differences between groups were noted in food efficiency.

In the F_1 generation among males at 1,750 ppm food consumption (data not shown) consistently decreased significantly (with the exception of days 77-84). It increased significantly at 10 ppm on days 84-91. Food efficiency (Table 4) decreased significantly at 1,750 ppm on days 91-98.

Among F_1 females food consumption (data not shown) decreased significantly at 10 ppm on days 91-98; at 250 ppm on days 7-14, 21-35, 56-63, 91-105, and 0-105; and at 1,750 ppm during the entire premating. During gestation, food consumption decreased consistently at 1,750 ppm. Food efficiency among females (Table 4) decreased significantly at 1,750 ppm on days 0-7, 21-28, and 0-70 and increased significantly at 10 ppm on days 70-77. During gestation no differences between groups were noted in food efficiency.

Compound intake: In the F_0 generation mean compound intake (corrected for purity) during the premating period was 0.58, 14.8, and 101 mg/kg/day for males and 0.71, 18.5, and 131 mg/kg/day for females at 10, 250, and 1,750 ppm, respectively. In the F_1 generation mean compound intake during the premating period was 0.77, 18.9, and 139 mg/kg/day for males and 0.88, 22.1, and 157 mg/kg/day for females at 10, 250, and 1,750 ppm, respectively. During gestation for F_0 and F_1 females it was 0.73, 18.2 and 128 mg/kg/day and 0.69, 16.4, and 116 mg/kg/day, respectively, for these same dosage groups.

Gross and microscopic pathology: No compound-related gross or histologic findings were observed for any sex and generation.

Testis weights: No compound-related effects were observed for any generation. At 1,750, relative (percent of body weight) testis weight significantly increased in both generation males, which was due to decreased body weight rather than caused by the test compound. An incidental significant increase was noted in absolute testis weight at 10 ppm in F_1 males.

Reproductive Toxicity: Compound-related reproductive effects were observed at 1,750 ppm. Summaries of these effects are presented in Tables 6 and 7. Detailed results are presented in the text.

In the F_0 generation the fertility index significantly increased at 1,750 ppm due to a low fertility index in the control group. Likewise, independently of the test material, the live birth index significantly increased at 1,750 ppm. Pup body weight for sexes combined (Table 6) or separated (not shown), significantly decreased at 1,750 ppm on lactation days 0, 4 (data not shown), 7, 14 (data not shown), and 21; this was considered to be a compound-related effect.

In the F_1 generation the gestation length significantly decreased at 250 ppm. Since this decrease did not occur in a dosage-related manner, it was considered incidental. Pup body weight for sexes combined (Table 6) or separated (not shown) significantly decreased at 1,750 ppm on lactation days 7, 14 (data not shown), and 21; this was considered to be a compound-related effect.

No compound-related clinical observations or gross malformations were noted in pups from any litter and generation.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses: Concentration, stability, and homogeneity of the test material in the diet were confirmed to be within ±15% of nominal values.

Parental Toxicity: Compound-related toxicity was observed at 1,750 ppm in both sexes and generations. It was manifested as significantly decreased body weight, body weight gain, and food consumption. The effect on these parameters at 10 and 250 ppm were considered to be incidental. No compound-related effects were noted in the rates of mortality and clinical, gross, and microscopical observations.

Based on these results, the parental toxicity NOEL and LOEL were 250 and 1,750 ppm, respectively.

Reproductive Toxicity: Compound-related reproductive toxicity was observed at 1,750 ppm. It was manifested in pups as significantly decreased body weight in both sexes and generations. No compound-related effects were noted in fertility indices, gestation length, pup survival, pup clinical observations, and pup anomalies.

Based on these results the NOEL and LOEL for reproductive toxicity were 250 mg/kg/day and 1,750 ppm, respectively.

E. CLASSIFICATION: CORE Guideline Data.

Parental toxicity NOEL = 250 ppm (approximately 18.6 mg/kg/day)
Parental toxicity LOEL = 1,750 ppm (approximately 132 mg/kg/day based on decreased body weight/body weight gain and food consumption)

Reproductive toxicity NOEL = 250 ppm (approximately 18.6 mg/kg/day)
Reproductive toxicity LOEL = 1,750 ppm (approximately 132 mg/kg/day based on decreased pup body weight)

F. RISK ASSESSMENT: Not Applicable

Table 1. Mean Body Weight Gain (g ± S.D.) During the Premating Period for Rats Fed Diuron for Two Successive Generations[a]

Study Days	Dietary Level (ppm)			
	0	10	250	1,750
F_0 Males				
0 - 7	45.9 ± 7.3	41.6 ± 7.5	47.6 ± 5.6	28.8 ± 10.3*
21 - 28	32.0 ± 8.2	32.2 ± 6.1	32.6 ± 6.7	27.3 ± 6.0*
42 - 49	27.9 ± 6.7	24.0 ± 9.8	25.3 ± 7.1	20.1 ± 5.8*
63 - 70	9.4 ± 9.8	14.0 ± 5.8*	14.9 ± 6.3*	13.6 ± 5.7*
0 - 70	254.2 ± 39.4	267.9 ± 37.1	272.0 ± 28.0	214.6 ± 26.3*
F_0 Females				
0 - 7	22.1 ± 7.0	31.1 ± 12.3*	24.2 ± 8.8	11.6 ± 7.2*
21 - 28	11.5 ± 9.4	10.3 ± 9.8	8.3 ± 6.8	3.6 ± 8.9*
42 - 49	8.9 ± 8.5	5.4 ± 10.2	8.3 ± 7.9	3.6 ± 6.5
63 - 70	3.0 ± 8.8	5.3 ± 8.0	5.1 ± 9.4	2.7 ± 7.5
0 - 70	98.8 ± 24.2	108.7 ± 28.1	98.0 ± 22.2	70.9 ± 15.2*
F_1 Males				
0 - 7	52.0 ± 4.8	49.7 ± 5.4	47.0 ± 14.2	40.6 ± 5.4*
21 - 28	70.0 ± 10.6	68.5 ± 8.4	67.7± 5.9	59.5 ± 6.8*
42 - 49	44.3 ± 12.5	41.6 ± 7.3	38.9 ± 9.8	35.3 ± 13.4*
63 - 70	31.3 ± 11.0	28.8 ± 11.2	24.0 ± 9.1*	23.2 ± 11.2*
91 - 98	21.0 ± 11.1	18.6 ± 7.9	17.0 ± 7.0	11.4 ± 6.0*
0 -105	580.9 ± 55.3	585.9 ± 49.6	565.7 ± 42.5	494.7 ± 57.8*
F_1 Females				
0 - 7	45.3 ± 5.6	43.9 ± 5.3	40.3 ± 7.2	34.8 ± 4.9*
21 - 28	27.7 ± 7.1	26.7 ± 6.2	27.2 ± 7.1	24.6 ± 5.8
42 - 49	13.8 ± 10.5	12.8 ± 9.2	13.6 ± 6.3	11.2 ± 8.1
63 - 70	8.4 ± 8.1	9.1 ± 8.4	12.2 ± 6.5	9.9 ± 5.2
91 - 98	7.4 ± 6.6	6.3 ± 11.8	4.6 ± 6.0	4.5 ± 6.0
0 -105	284.3 ± 35.7	285.5 ± 36.8	267.9 ± 39.8	245.8 ± 21.6*

[a]Data were extracted from Study No. HLR 560-90, Tables 4, 5, 8, and 9.

*Significantly different from control ($p \leq 0.05$)

Table 2. Mean Body Weight Gain (g ± S.D.) During Gestation for Rats Fed Diuron for Two Successive Generations[a]

	Dietary Level (ppm)			
Gestational Days:	0	10	250	1,750
F_0 Generation - F_1 Litters				
0 - 7	33.3 ± 13.1	34.7 ± 11.3	35.4 ± 12.5	29.0 ± 7.8
7 - 14	33.3 ± 11.0	33.3 ± 9.6	29.5 ± 11.1	29.4 ± 8.3
14 - 21	86.6 ± 17.5	80.9 ± 36.3	89.3 ± 17.6	82.6 ± 11.7
0 - 21	153.3 ± 23.5	148.9 ± 38.1	154.2 ± 17.8	141.0 ± 15.2
F_1 Generation - F_2 Litters				
0 - 7	32.3 ± 22.2	26.4 ± 31.2	28.9 ± 13.4	26.2 ± 8.5
7 - 14	28.4 ± 15.4	39.9 ± 31.3	34.8 ± 13.9	25.8 ± 9.7
14 - 21	89.9 ± 21.6	86.4 ± 22.2	89.9 ± 23.1	71.0 ± 22.0*
0 - 21	150.6 ± 37.8	152.7 ± 23.6	154.5 ± 28.4	122.3 ± 26.9*

[a]Data were extracted from Study No. HLR 560-90, Table 11.

*Significantly different from control ($p \leq 0.05$)

Table 3. Mean Body Weight Gain (g ± S.D.) During Lactation for Rats Fed Diuron for Two Successive Generations[a]

Lactational Days:	Dietary Level (ppm) 0	10	250	1,750
F_0 Generation - F_1 Litters				
0 - 7	14.9 ± 18.1	12.3 ± 26.1	22.7 ± 18.6	29.5 ± 16.3*
7 - 14	8.7 ± 17.8	-0.3 ± 26.1	0.2 ± 20.9	3.4 ± 28.3
14 - 21	-48.8 ± 21.0	-33.5 ± 30.9	-31.8 ± 23.9	-33.6 ± 26.7
0 - 21	-25.1 ± 20.4	-21.5 ± 22.4	-8.9 ± 19.7	-0.8 ± 27.5*
F_1 Generation - F_2 Litters				
0 - 7	3.6 ± 23.2	1.8 ± 20.6	12.2 ± 16.3	30.1 ± 21.2*
7 - 14	5.3 ± 21.2	4.3 ± 18.0	4.8 ± 10.8	3.3 ± 18.2
14 - 21	-20.4 ± 22.7	-17.7 ± 24.5	-14.5 ± 16.4	0.9 ± 17.9*
0 - 21	-11.5 ± 30.3	-11.7 ± 24.2	2.6 ± 25.2	34.1 ± 20.2*

[a]Data were extracted from Study No. HLR 560-90, Table 13.

*Significantly different from control ($p \leq 0.05$)

Table 4. Mean Food Efficiency (g weight gain/g food consumed ± S.D.) During the Premating Period for Rats Fed Diuron for Two Successive Generations[a]

Study Weeks	Dietary Level (ppm)			
	0	10	250	1,750
F_0 Males				
0 - 7	0.222 ± 0.026	0.206 ± 0.035	0.231 ± 0.021	0.164 ± 0.054*
21 - 28	0.146 ± 0.034	0.146 ± 0.023	0.147 ± 0.024	0.153 ± 0.065
42 - 49	0.132 ± 0.025	0.111 ± 0.046*	0.113 ± 0.026	0.103 ± 0.027*
63 - 70	0.044 ± 0.044	0.066 ± 0.025*	0.070 ± 0.028*	0.068 ± 0.028*
0 - 70	0.120 ± 0.011	0.125 ± 0.011	0.126 ± 0.007	0.110 ± 0.011*
F_0 Females				
0 - 7	0.149 ± 0.041	0.210 ± 0.075*	0.161 ± 0.052	0.084 ± 0.048*
21 - 28	0.072 ± 0.056	0.065 ± 0.063	0.053 ± 0.043	0.024 ± 0.068*
42 - 49	0.060 ± 0.056	0.035 ± 0.070	0.054 ± 0.051	0.026 ± 0.047
63 - 70	0.020 ± 0.063	0.035 ± 0.055	0.031 ± 0.058	0.019 ± 0.056
0 - 70	0.066 ± 0.011	0.074 ± 0.015*	0.066 ± 0.011	0.051 ± 0.010*
F_1 Males				
0 - 7	0.454 ± 0.057	0.422 ± 0.054	0.433 ± 0.139	0.442 ± 0.069
21 - 28	0.349 ± 0.054	0.337 ± 0.037	0.341 ± 0.025	0.335 ± 0.030
42 - 49	0.200 ± 0.039	0.188 ± 0.031	0.179 ± 0.042	0.176 ± 0.054
63 - 70	0.138 ± 0.043	0.127 ± 0.049	0.112 ± 0.037	0.118 ± 0.057
91 - 98	0.093 ± 0.040	0.082 ± 0.034	0.079 ± 0.032	0.060 ± 0.032*
0 -105	0.189 ± 0.009	0.188 ± 0.013	0.188 ± 0.008	0.182 ± 0.014
F_1 Females				
0 - 7	0.417 ± 0.057	0.403 ± 0.052	0.400 ± 0.063	0.408 ± 0.084
21 - 28	0.180 ± 0.042	0.173 ± 0.037	0.192 ± 0.047	0.188 ± 0.050
42 - 49	0.089 ± 0.067	0.083 ± 0.056	0.095 ± 0.044	0.082 ± 0.060
63 - 70	0.052 ± 0.052	0.060 ± 0.054	0.079 ± 0.039	0.073 ± 0.039
91 - 98	0.043 ± 0.037	0.023 ± 0.134	0.029 ± 0.040	0.032 ± 0.044
0 -105	0.124 ± 0.013	0.128 ± 0.011	0.126 ± 0.012	0.126 ± 0.010

[a]Data were extracted from Study No. HLR 560-90, Tables 16, 17, 20, and 21.

*Significantly different from control ($p \leq 0.05$)

Table 5. Mean Food Efficiency (g weight gain/g food consumed ± S.D.) During Gestation for Rats Fed Diuron for Two Successive Generations[a]

Gestational Days:	Dietary Level (ppm) 0	10	250	1,750
F_0 Generation - F_1 Litters				
0 - 7	0.187 ± 0.066	0.194 ± 0.062	0.199 ± 0.070	0.177 ± 0.047
7 - 14	0.166 ± 0.036	0.165 ± 0.035	0.153 ± 0.046	0.176 ± 0.075
0 - 14	0.178 ± 0.027	0.179 ± 0.024	0.177 ± 0.028	0.174 ± 0.031
F_1 Generation - F_2 Litters				
0 - 7	0.130 ± 0.365	0.168 ± 0.150	0.180 ± 0.074	0.183 ± 0.056
7 - 14	0.114 ± 0.245	0.227 ± 0.221	0.202 ± 0.086	0.156 ± 0.061
0 - 14	0.121 ± 0.306	0.182 ± 0.022	0.189 ± 0.082	0.166 ± 0.027

[a]Data were extracted from Study No. HLR 560-90, Table 23.

Table 6. Summary of Effects of Dietary Administration of Diuron on F_1 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	10	250	1,750
No. matings (F_0 parents)	30	30	30	30
Mating index (%)[b]	93	100	97	100
Fertility index (%)[c]	79	83	79	98*
Gestation index (%)[d]	100	96	100	100
Gestation length (days)	22.9	22.6	22.8	22.6
No. females with liveborn pups	21	25	23	29
Total no. live pups				
Day 0	300	348	342	417
Day 4 precull	296	328	338	411
Day 21	167	181	181	229
Mean no. live pups/litter				
Day 0	14.3 (21)[e]	13.9 (25)	14.9 (23)	14.4 (29)
Day 4 precull	14.1	14.3 (23)	14.7	14.2
Day 21	8.0	7.9	7.9	7.9
Live birth index (%)[f]	97	96	98	99*
Viability index (%)[g]	99	99	99	99
Lactation index (%)[h]	100	99	100	99
Mean pup body weight (g)				
Day 0	7.0	7.0	7.0	6.6*
Day 7	19.1	19.7	18.3	16.2*
Day 21	58.9	61.3	57.9	48.4*
Sex ratio (% male day 0)	49	53	58	48

[a]Data were extracted from Study No. HLR 560-90, Tables 37-40.

[b]Mating index: No. sperm-positive females expressed as % of total No. mated females

[c]Fertility index: No. females delivering a litter expressed as % of No. sperm-positive females

[d]Gestation index: No. females delivering a live litter expressed as % of No. females delivering a live or dead litter

[e]Number of litters

[f]Live birth index: Percentage of pups born alive based on No. of total pups born

[g]Viability index: Percentage of pups surviving four days based on No. of live pups born

[h]Lactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull

*Significantly different from control ($p \leq 0.05$)

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Table 7. Summary of Effects of Dietary Administration of Diuron on F_2 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm)			
	0	10	250	1,750
No. matings (F_1 parents)	30	30	30	30
Mating index (%)[b]	97	87	93	93
Fertility index (%)[c]	90	77	82	86
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.6	22.7	22.1*	22.5
No. females with liveborn pups	26	20	23	23
Total no. live pups				
Day 0	340	280	309	275
Day 4 precull	324	276	306	289
Day 21	187	157	176	181
Mean no. live pups/litter				
Day 0	13.1 (26)[e]	14.0 (20)	13.4 (23)	12.5 (22)
Day 4 precull	12.5	13.8	13.3	12.6 (23)
Day 21	7.2	7.8	7.7	7.9
Live birth index (%)[f]	96	99	96	99
Viability index (%)[g]	96	99	99	99
Lactation index (%)[h]	98	99	100	100
Mean pup body weight (g)				
Day 0	6.7	7.0	6.9	6.5*
Day 7	18.7	19.6	18.8	16.6*
Day 21	62.7	64.7	61.1	51.1*
Sex ratio (% male day 0)	52	49	53	51

[a]Data were extracted from Study No. HLR 560-90, Tables 37-39 and 41.

[b]Mating index: No. sperm-positive females expressed as % of total No. mated females

[c]Fertility index: No. females delivering a litter expressed as % of No. sperm-positive females

[d]Gestation index: No. females delivering a live litter expressed as % of No. females delivering a live or dead litter

[e]Number of litters

[f]Live birth index: Percentage of pups born alive based on No. of total pups born

[g]Viability index: Percentage of pups surviving four days based on No. of live pups born

[h]Lactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull

*Significantly different from control ($p \leq 0.05$)